EUROPEAN FEDERATION OF
PHARMACEUTICAL INDUSTRIES
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FÉDÉRATION EUROPÉENNE
D'ASSOCIATIONS ET D'INDUSTRIES
PHARMACEUTIQUES

Ref: SC.sr/58.556 **October 29th, 2003**

Dockets Management Branch (HFA – 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
USA

Dear Sir/Madam,

Re: EFPIA Comments on Draft Guidance for Industry on Providing Regulatory Submissions in electronic Format – Human Pharmaceutical Product Applications and Related Submissions [Docket No 2003D-0367]

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Its mission is to promote pharmaceutical research and development in Europe. Founded in 1978, its members consist of 18 national pharmaceutical industry associations and 43 pharmaceutical companies involved in the research, development and manufacturing of medicines for human use. Our membership also includes national industry associations in the acceding countries, i.e. the 10 countries which will join the European Union as from May 2004.

The comments submitted in this document have been written by EFPIA Product and Regulatory Information Management Ad Hoc Group (PRIMAG AHG).

EFPIA welcomes the opportunity to comment and appreciates the effort that has gone into the definition of the guidance and associated specifications. However, there are several areas of significant concern and many areas where specific detail is lacking and clarification is needed. These are detailed in the attached document.

We thank you in advance for giving due consideration to our comments.

Yours faithfully,

Stéphane Callewaert
Scientific, Technical and Regulatory Affairs

Encl.: EFPIA comments

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EFPIA Comments
on

Draft Guidance for Industry on Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions

[Docket No. 2003D-0367]

Introduction

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Its mission is to promote pharmaceutical research and development in Europe. Founded in 1978, its members consist of 18 national pharmaceutical industry associations and 43 pharmaceutical companies involved in eth research, development and manufacturing of medicines for human use. Our membership also includes national industry associations in the acceding countries i.e. the 10 countries which will join the European Union as from May 2004.

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EFPIA welcomes the opportunity to comment and appreciates the effort that has gone into the definition of the guidance and associated specifications. However, there are several areas of significant concern and many areas where specific detail is lacking and clarification is needed. These are identified below, with reference to each of the individual documents making up the guidance.

1. Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Substances

On Page 3, Line 91, states "each document should be provided as a separate file." The definition of a document should be clarified. It appears in the second paragraph that they mean that the lowest heading in the hierarchy equates to a document, however, that is an inference. This is in conflict with the current understanding that clinical and nonclinical documents should be granular. Should documents be split (synopsis, body, appendices) or contained as one file per document. This appears to be the case for clinical as stated in this document. A statement should be added here identifying that Module 5 would have granular study reports based on ICH E3 guidance.

On Page 3, Line 98 of this draft guidance it is unclear whether this is referring to a physical TOC for inclusion in the application. The eCTD specification has deliberately omitted a physical TOC, namely there is no CTD sections 2.1, 3.2, 4.1 or 5.1 since it is intended that the backbone provide the contents and navigation for the submission. The TOC section of the guidance is useful because it will assist the applicant in defining at what level documents are placed. However, the guidance should clarify whether a TOC is being required or not in the submission itself. It should not be needed.

On Page 4, Line 163 it is unclear whether the CFR sections quoted in the footnote covers this guidance. It is unclear whether it is possible to refer between one submission and another e.g. from the NDA to the IND or from one NDA to another. Theoretically this would work but the review tool does not support this. The guidance should be made clearer and not include items that are not currently supported by the agency's systems.

On Page 5, Line 197 the guidance should be strengthened to positively discourage a paper submission. As previously stated at the DIA meeting in August 2003, the FDA does not want paper copies if electronic copies are submitted because of potential discrepancies. The "are not needed" statement may be misinterpreted and suggest that paper copies are up to the discretion of the applicant.

On Page 6, Line 212 it is recommended that the applicant consider using OCR in order to provide textual information with pivotal studies that are not available electronically. There needs to be clarification regarding the quality of the OCR that is acceptable since it is extremely resource intensive to achieve 100% accuracy. In order to use OCR technology, the entire process must be validated in order to be compliant with 21 CFR Part 11. Due to current technology and the extensive use of scientific symbols in regulatory documentation, this option may not be feasible for most companies and the cost to implement is rather high.

On Page 6, Line 223 further clarification is needed. There are several ways in which an esignature can be done. Some esignature solutions present the signature as a separate but intimately related file. However, since the backbone supports only a PDF file then how would the backbone handle a separate file?
If electronic signature technology is not available, can these forms be scanned as PDF and included in the submission, providing the originals with the submission?

On Page 6, Line 237 it would be useful to include "and no spaces" since this is part of the eCTD specification. Applicants could interpret that spaces are allowed but they're not.

On Page 6, Line 246 the convention of file naming is equally applicable to folder names and should be included.

On Page 7, Line 294. The way the link should be defined should be clarified in more detail e.g. is the path ....\...\...\ a default? More specific detail should be provided.

On Page 8, Line 310 states that the FDA is able to accept submissions using secure e-mail; however, they do not indicate what the e-mail address is nor do they reference a guidance that does.

On Page 9, Line 354. It should be clarified whether the paragraph numbering scheme translates into a specific folder numbering scheme i.e. should the folders be numbered 1.1, 1.2, 1.3, and so on. The ICH guidance gives specific folder numbering scheme for Modules 2 – 5.

Page 13, Line 536 several comments are noted regarding the Study Reports. Firstly, the eCTD specification suggests that breaking down a report is only relevant for large reports such as carcinogenicity reports. This should also be stated here. Multiple files should be avoided where possible.

On Page 13, Line 538 This section is confusing. It states that study reports should be provided as single documents, but where they are does provide a structure for breaking them out. However, it then includes a section for Legacy Study Reports that are prepared as single documents. This appears contradictory.

Secondly, FDA is defining a breakdown of a preclinical study report - which is setting a precedent. This is a matter that is pan-regional and so should be considered at ICH.

Thirdly, this list is not entirely relevant. It would appear to be a cut down version of the clinical study report which leads to a number of inconsistencies such as

- signatures should be relate to a 'study director' in a preclinical study
- important publications referenced in this report should be part of 4.3 Key references and not the report.
- 'Individual subjects listings' - should be 'animals'
- Compliance' is not relevant to a preclinical study.

Fourthly, 'legacy study report' is not relevant because that should be the default for this type of report since 'typically, a single document should be provide...'

The whole list needs to be reviewed at ICH, in conjunction with CTD-S and revised.

Page 14, Line 569. Practice of many sponsors is currently not to submit the protocol for a preclinical study but to provide a summary in the main body of the report. Industry would like to produce a single study report output worldwide and this would be a single file. It could be interpreted by this guidance that submission of the protocol is now required in the US which would mean that something specific for the US would need to be produced. This is something that should be discussed at ICH before being included in a regional guidance.

Page 14, Line 572. The whole aspect of the study director's statement and the applicability of the signature need to be assessed. At present the signature is applicable to the single file supplied. If additional files are supplied then what does the original signature apply to? There is a potential that the GLP Inspectors might have a differing view from the reviewers. This should be clarified.

Page 14, Line 576. In the example provided, it obvious that a SAS file and a PDF file would be a separate file. A better example where files should be provided separately should be used.

Page 14, Line 580. We had assumed that an STF would have to be provided for all studies whether there is one file or more associated with the study. The reason for this is that in order to make use of the route of administration and species information, then it would have to be defined as part of the STF. There would be little value in putting such metadata against only multiple file documents. It should be done for all or none.

Page 14, Line 590. The location of the datasets is not consistent with the ICH specification. This calls for datasets with the study report, not located together. At present the datasets are only a requirement for the US but it is something that should be It should be agreed at the ICH level since it will require a change to the specification. The FDA approach is not problematic; however, but it is setting a precedent.

On Page 15, Line 614 states to "provide the tabular listing of all clinical studies as a single PDF file." Does that mean that the applicant is expected to compile a comprehensive tabular listing that includes all the clinical studies rather than providing the listings by study? If this is the case, is it also expected that a listing specific to each study as broken out in Section III.E.2?

Page 15, Line 619. The STF should be used for all studies including legacy studies since there would be little value in the provision of metadata such as 'type of control' if it is not applied to all studies.

Page 15, Line 626. Legacy Study Report should be broken out as something separate from the list - it is the study report when things are not typical.

Page 16, Line 666. It should be possible to define additional appendices that are beyond E3 specified appendices. Typical ones that are used in the industry are:

Bioanalytical Results
Certificates of Analysis
Pharmacokinetic or Population Pharmacokinetic report
Biomarker report
Pharmacogenetic Results
Health Outcomes report on direct cost data
Virology Genotypic and Phenotypic Results

but these don't fit into any of the classifications defined by this guidance. There needs to be the ability to include these.

On Page 16, Line 667. It should be clarified whether there is specific guidance that covers the generation of electronic case report forms. The guidance should be referenced in this paragraph including how PDF file should be created e.g. whether screen shots are an acceptable format for submission.

On Page 16, Line 676 it states that the "title of the document" should include the subject's unique ID. Do this mean the title field in the PDF Document Summary or the title element in the XML?

Page 16, Line 686 The location of CRF files is not consistent with the ICH specification. Whilst we do not a have a problem with the specifics of the proposal, it should be agreed via ICH, as the specification will need to change.

2. FDA Module 1 Specifications

Page 6 - Is the example of the sequence actually plausible? Under sequence 0007 there is an amendment to the original application but in order to have a supplement 0003 then the original application would have been approved and so you would not be able to make an amendment to an approved application - it would be a supplement. Please clarify?

Page 13 - Is the structure of the IND annual report to be the same as for the NDA? It would appear that the IND annual report structure is not adequately covered by this specification. Further clarification is requested.

Page 38 is blank.

This is not related to the integrity of this document; however, attention should be given to the file path that is identified in the footer.

3. FDA Modules 2-5 Specifications

On Page 3, in the Table, it states that the "modified-file attribute" provides the location of a previously submitted document and the "action this document has on it." However, in Section II.C.4, it appears that the "modified-file" attribute only provides the location of a previously submitted document, it does not actually provide the action to it. That appears to be provided by the "operation" attribute.

Page 5, Lines 163. This has made the leaf id mandatory whereas at ICH it was optional. Recent ICH Q&As have made it mandatory because FDA has made it mandatory in this guidance. As a process it would have been better to take this to ICH for consideration first.

Page 5, Line 176. It would be useful to give some examples of how the operation attribute should be used under specific circumstances.

Page 6, Line 184. The modified file attribute is used by referring to the ID attribute of the file being modified and not the relative path, as specified in the ICH Specification (page 6-8). This is changed within the FDA specification and should be agreed by ICH before adoption at a regional level. This guidance should not contain this until ICH has approved.

It is not clear whether empty leaf elements should be included or not. Some examples include them, some don't. Some examples routinely include the same empty leafs, but not others. Clarification as to whether leaf elements are optional if empty (or if they are required for some but optional for others) would be helpful.

4. FDA eCTD Table of Contents Headings and Hierarchy

There needs to be clarification as to whether there is the expectation for a physical table of contents. It would be useful to take the appropriate sections from the Draft Guidance (when clarified) and repeat them, as an introduction here so that it is clear that this is defining the lowest level of granularity that might be used (but in the Preclinical part in particular this is not expected to be used).

Page 12, Study Report - It is not sensible to put this breakdown under a primary Pharmacodynamic study since it would not contain much of what is listed here. A better example to place this under would be a Toxicology Study.

Module 4, Study Reports, Pharmacology (pages 13-16) refer to "4.2.1 Primary Pharmacodynamic", but "Primary Pharmacodynamic "is not numbered in this document.

E3 section numbers are not appropriate for a preclinical study - shows that the list has been produced by someone who doesn't appreciate the content of such studies.

Page 13 – 16. Reference is repeatedly made to 4.2.1.1 but since the TOC is un-numbered this is not appropriate.

Page 13. Analytical methods and validation reports. The reference to 4.2.1.1 is even more tenuous because this type of report would contain none of the data that is specified.

Page 16. It is unlikely that a Bioavailability study will contain the E3 appendices. It would be better to put this example under one of the Efficacy sections.

Page 22 CRFs. CTD section 5.3.7 is missing. Does this mean that the CRFs are to be filed with the Study Report. This is amending the CTD spec and hence is not consistent with the eCTD spec. Such a change needs to be taken through ICH.

Module 5, Page 21. Clinical Study Reports- Misspelling in the second bulleted item, "non standardizes method" should be corrected to "non standardized method."

5. Study Tagging Files Specifications

This document is very hard to understand. Most colleagues in the industry are having a difficult time trying to interpret this document. This concepts explained in this document could be explained in a easier format. Part of the design is based upon the premise that there will be a single backbone globally whereas in reality there will be a regional specific submission for every product. This over complicates the design of the STF.

There is duplication between the eCTD backbone and STF. It may be better to put the information into the backbone.

Metadata is being validated by the style sheets and these could be regional. This is problematic from two positions. One, it is considered bad design to write into a style sheet as that should only deal with format, content should be defined by the DTD. Two, pick lists should be managed at the ICH level to ensure consistency. Whilst the STF is only being required at present by FDA it is setting a precedent, which may not be acceptable across all regions. We may end up with different approaches which must be avoided.

Route of administration choices are not adequate. There are many routes that are not included including those that many pharmaceutical companies regularly use e.g. intranasal.

The European Union needs the ability to specify that certain appendices are available on request, potentially as metadata. Additional appendices must be also able to be specified.

Whilst it is known that a long-term solution is being considered at ICH, in the short term the following should be addressed with this form of the STF

1. An expanded list of routes of administration
2. The ability to define additional appendices types to cover ones over and above the E3 defined appendices.

Page 4 is blank.

6. Annual Reports for New Drug Applications and Abbreviated New Drug Applications

The guidance should proscribe the file names for the additional files to be provided in the Annual Report that are not covered by other guidance documents.

EFPIA, 27 October 2003.